ORIGINAL ARTICLE

Recent Improvements in Survival in Primary Systemic Amyloidosis and the Importance of an Early Mortality Risk Score

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OBJECTIVE: **To examine whether the outcome of patients with primary systemic amyloidosis (AL) has improved over time and to identify predictors of early mortality in patients with AL.**

PATIENTS AND METHODS: **We studied 2 separate cohorts of patients. The first cohort, consisting of 1998 patients with AL seen at Mayo Clinic between January 1977 and August 2006, was used to examine the trends in overall survival (OS) from diagnosis during this 30-year period. The second cohort, consisting of 313 patients seen between September 2006 and August 2009, was used to validate a model for predicting early mortality.**

RESULTS: **The 4-year OS from diagnosis improved during each decade of follow-up: 21%, 24%, and 33%, respectively, for the periods 1977-1986, 1987-1996, and 1997-2006 (*P*<.001). Within the last group (1997-2006), 4-year OS during 1997-1999, 2000-2002, and 2003-2006 was 28%, 30%, and 42%, respectively (*P*=.02). However, the 1-year mortality remained high during the 30-year period. A risk stratification score using cardiac troponin T, N-terminal pro-brain natriuretic peptide, and uric acid identified patients at risk of early mortality. The 1-year mortality with 0, 1, 2, or 3 risk factors was 19%, 37%, 61%, and 80%, respectively, in this training cohort of 459 patients. This was confirmed in a validation cohort of 313 patients.**

CONCLUSION: **Survival in AL has improved over time, with maximum improvement occurring in the past decade. However, early mortality remains high, and prospective identification of patients at risk of early mortality may allow development of risk-adapted strategies.**

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AL = primary systemic amyloidosis; CI = confidence interval; cTnT = cardiac troponin T; NT-proBNP = N-terminal pro-brain natriuretic peptide; OS = overall survival; SCT = stem cell transplant

Primary systemic, or light-chain, amyloidosis (AL) is a clonal plasma cell disorder characterized by a relatively low plasma cell burden and multiorgan deposition of immunoglobulin light-chain–derived amyloid fibrils.[1-5] Although amyloid fibrils can originate from more than 25 different proteins, AL is the most common form of amyloidosis. The survival of patients with amyloidosis is quite variable, with median survival ranging from 12 to 18 months in different series, and largely depends on the number of organs involved and the severity of their involvement.[1,2,6] High-dose therapy and stem cell transplant (SCT) have been increasingly used for treatment of this disease, and case-control studies suggest an improved outcome, although this modality is an option only for a minority of patients.[6-11] Treatment of amyloidosis has typically followed developments in therapy for multiple myeloma, in which a marked shift in treatment approaches has occurred because of the availability of several effective new drugs in the past 10 years.[12] These changes have improved survival in patients with myeloma during the past decade.[13] In addition to new drugs, the combination of melphalan and dexamethasone is an effective regimen for AL, and risk-adapted approaches to SCT have decreased treatment-related mortality.[14-24] Whether recent progress in risk stratification and treatment approaches has translated into improved survival for these patients is unclear. Therefore, we undertook this study to examine trends in survival of patients with AL over time, with an emphasis on identifying patient characteristics predicting outcome.

PATIENTS AND METHODS

We studied 2 separate cohorts of patients. The first cohort, consisting of 1998 patients with AL seen at Mayo Clinic between January 1977 and August 2006, was used to examine the trends in overall survival (OS) from diagnosis during this 30-year period. The second cohort, consisting of 313 patients seen between September 2006 and August 2009, was examined only for the changes in early mortality and for validation of a model for predicting early mortality developed from the first cohort of patients. Patients in the first cohort were initially divided by their date of diagnosis into 3 groups, each at 10-year intervals (1977-

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1986, 1987-1996, and 1997-2006). We further divided the cohort of patients seen during the last decade studied (1997-2006) into 3 subgroups to evaluate changes during this recent period.

Data regarding these patients were extracted from prospectively maintained databases and review of medical records. Follow-up information on these patients was collected prospectively and entered at the time of each visit. For patients followed up at other institutions, annual follow-up letters were sent to patients to inquire about their disease status. All patients had consented to the use of their medical records, and the study was conducted in accordance with institutional guidelines, with the approval of the Mayo Clinic Institutional Review Board, and in accordance with the principles of the Declaration of Helsinki.

Data on cardiac biomarkers troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were available in a subset of patients, with tests performed either as part of clinical care or on stored frozen serum as part of previous studies. Tests for cTnT were performed with sensitive second- and third-generation assays with reagents provided by Roche Diagnostics (Indianapolis, IN) and Siemens Healthcare Diagnostics (Deerfield, IL). Levels of NT-proBNP were measured with an electrochemiluminescence sandwich immunoassay (Roche Diagnostics) on an Elecsys System. Serum uric acid results were obtained from patient records, and tests were performed by standard assays (Roche Diagnostics). The reference range is 4.3 to 8.0 mg/dL (to convert to μmol/L, multiply by 59.485) in men and 2.3 to 6.0 mg/dL in women, with the levels in women tending to reach those in men after menopause.

Kaplan-Meier analysis was used to estimate OS, and differences between groups were tested for statistical significance using the 2-tailed log-rank test.[25] Overall survival was defined as the time from the date of initial diagnosis of AL to the date of death or last follow-up. In order to identify risk factors for early mortality, logistic regression was used for each of the variables, and all available data were used to identify the best cutoff. Only patients with a minimum of 1 year of follow-up if alive at last contact or who had died within 1 year were included for the logistic regression. Each variable was then dichotomized using the cutoff and entered into a multivariate model, and the variables to be included in the final model were arrived at using a stepwise regression. Statistical analysis was performed using JMP 8.0 software (SAS Institute, Cary, NC), and the survival curves were generated using GraphPad Prism (GraphPad Software, La Jolla, CA).

RESULTS

Of the 1998 patients included in the study, 1262 (63%) were men. The estimated median follow-up for the entire cohort was 7.5 years (95% confidence interval [CI], 6.9-8.1 years), and the median OS from diagnosis was 1.3 years (95% CI, 1.1-1.4 years). The median follow-up of the 399 patients (20%) alive at last follow-up was 3.2 years (range, 0.01-26.0 years). The patients were divided into 3 cohorts on the basis of date of diagnosis: 1977-1986 (n=345), 1987-1996 (n=636), and 1997-2006 (n=1017). The baseline characteristics of the groups are presented in Table 1. The median OS from diagnosis for the 3 cohorts was 1.2, 1.2, and 1.5 years, respectively (P<.001; Figure 1, A). More importantly, steady improvement in long-term survival occurred among these patients, with 4-year survival estimates of 21%, 24%, and 33%, respectively. We also analyzed the survival outcomes within this group after excluding 207 patients who had received SCT at any time during the course of their disease. The improvements in outcome seen over time were similar among the remaining 1791 patients (P<.001; Figure 1, B). Next, we specifically looked at the survival trends within the last cohort (1997-2006), dividing the patients by 3 time periods: 1997-1999 (n=263), 2000-2002 (n=291),

TABLE 1. **Comparison of Baseline Characteristics Among Patient Groups**[a,b]

	1977-1986	1987-1996	1997-2006	P value[c]
Septal thickness (mm)	14 (7-30)	14 (7-30)	13 (7-38)	.04
Ejection fraction (%)	59 (15-78)	60 (8-84)	62 (9-86)	<.001
Alkaline phosphatase (× ULN)	0.7 (0.2-8.0)	0.8 (0.2-22.0)	0.8 (0.2-23.0)	<.001
Creatinine (mg/dL)	1.2 (0.6-14.0)	1.2 (0.4-12.0)	1.2 (0.5-14.0)	.5
Serum uric acid (mg/dL)	6.6 (1.8-17.5)	6.4 (2.3-17.5)	6.7 (1.3-17.5)	.07
Total bilirubin (mg/dL)	0.5 (0.2-7.1)	0.5 (0.1-25.0)	0.6 (0.1-34.0)	<.001
Serum albumin (g/dL)	2.9 (0.8-4.2)	2.9 (0.9-4.7)	2.9 (0.6-4.9)	.7
Urine albumin excretion (g/24 h)	0.6 (0-14.6)	0.6 (0-19.6)	0.4 (0-16.0)	.02

[a] ULN = upper limit of normal. Data are provided as median (min-max).
[b] SI conversion factors: To convert creatinine values to μmol/L, multiply by 88.4; to convert serum uric acid values to μmol/L, multiply by 59.485; to convert total bilirubin values to μmol/L, multiply by 17.104; to convert serum albumin values to g/L, multiply by 10.
[c] Wilcoxon signed rank test.

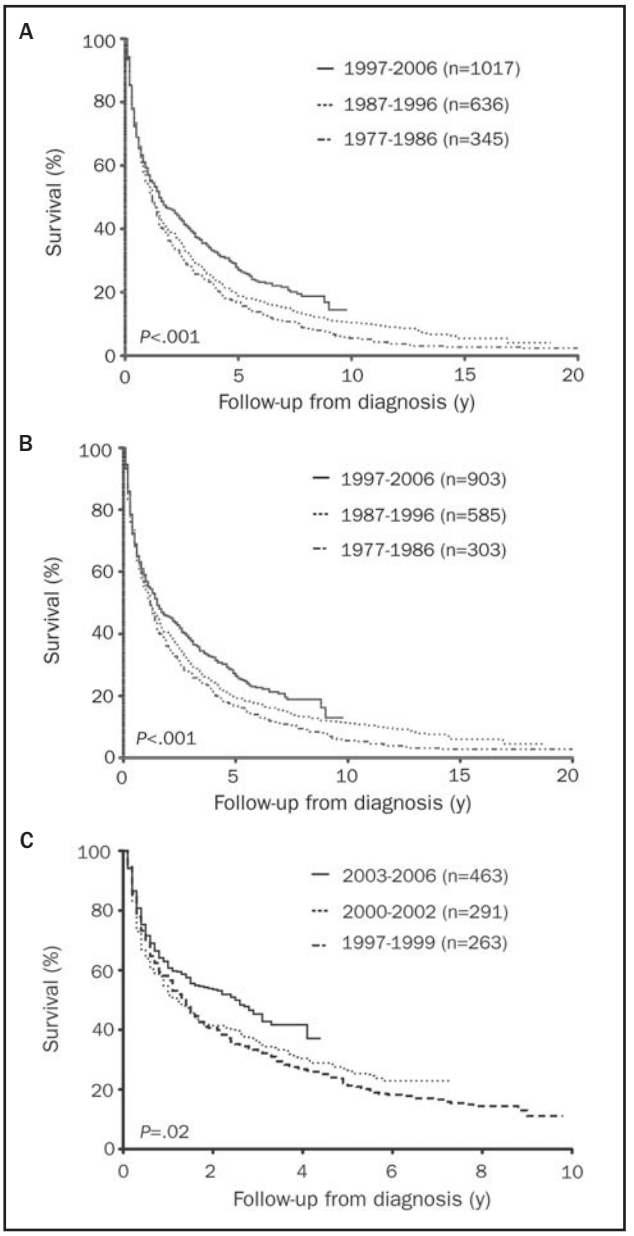

FIGURE 1. A, Overall survival (OS) from diagnosis among 1998 patients with primary systemic amyloidosis (AL), divided into 3 cohorts on the basis of date of diagnosis: 1977-1986 (n=345), 1987-1996 (n=636), and 1997-2006 (n=1017). The median OS from diagnosis for the 3 groups was 1.2, 1.2, and 1.5 years, respectively. The 4-year survival estimates for the 3 groups were 21%, 24%, and 33%, respectively (*P*<.001). B, Overall survival from diagnosis among patients with AL diagnosed during three 10-year periods, excluding those who received stem cell transplant at any time during the course of the disease. This group included 1791 patients: 1977-1986 (n=303), 1987-1996 (n=585), and 1997-2006 (n=903). Median OS for the 3 groups was 1.2, 1.2, and 1.4 years, respectively (*P*<.001). C, Overall survival from diagnosis among patients with AL diagnosed during 1997-2006 (n=1017), divided into 3 groups according to date of diagnosis: 1997-1999 (n=263), 2000-2002 (n=291), and 2003-2006 (n=463). The 4-year OS from diagnosis for the 3 groups was 28%, 30%, and 42%, respectively (*P*=.02).

and 2003-2006 (n=463). Although the OS from diagnosis was relatively unchanged between the first and second time periods (28% vs 30% 4-year survival), significant improvement occurred in the last 3-year period (42% survival at 4 years; *P*=.02; Figure 1, C).

Patients with advanced organ involvement by AL, especially cardiac involvement, have a very poor outcome. The current prognostic system uses cTnT and NT-proBNP to divide patients into 3 groups with very different outcomes.[26] The staging system uses a cutoff value for NT-proBNP of less than 332 ng/L and a cutoff value for cTnT of less than 0.035 μg/L. Depending on whether values were both low, high for only one, or high for both, patients were classified as having stage I, II, or III disease, respectively. To better understand whether the improvement in survival benefited all patients, we identified from among the 1998 patients a set of 491 in whom both these results were available for disease staging. The median OS from diagnosis for this group of patients was 1.5 years (95% CI, 1.2-2.1 years), and the median survival for stages I, II, and III was 4.0, 2.4, and 0.5 years, respectively (*P*<.001; Figure 2, upper left). The median OS of this group was not different from that of the remaining 1507 patients seen during the same time period; median OS for the latter group was 1.2 years (log-rank *P*=.10). We divided this set of 491 patients into 3 equal groups on the basis of the date of diagnosis. The earliest group of patients (group A, n=164) received their diagnosis during 1987-1996; the second group (group B, n=164), during 1996-2004; and the most recent group (group C, n=163), during 2004-2006. We examined the trend in OS over time within each stage by comparing groups A, B, and C. Among the patients with stage I disease, the median OS was not reached for group B or C and was 2.3 years (95% CI, 1.4-3.3 years) for group A (Figure 2, upper right). Among patients with stage II disease, the median OS was not reached for group C and was 2.4 years (95% CI, 1.2-3.2 years) for group B and 0.9 year (95% CI, 0.5-1.1 years) for group A (Figure 2, lower left). Finally, among patients with stage III disease, group C had a median OS of 1.0 year (95% CI, 0.5-1.9 years) compared with 0.4 year for both group A and group B (*P*<.001; Figure 2, lower right).

It was clear from the survival curves in Figure 1, A that the improvement in survival observed in these groups was not evident until after a year of follow-up, indicating the continued problem with early mortality in patients with AL. Therefore, we specifically examined the 1-year mortality among the entire patient cohort. The 1-year mortality was 44%, 46%, and 43%, respectively, during 1977-1986, 1987-1996, and 1997-2006, suggesting no clear improvement over time. We then examined the factors that might predict the likelihood of death within 1 year of diagnosis. Using

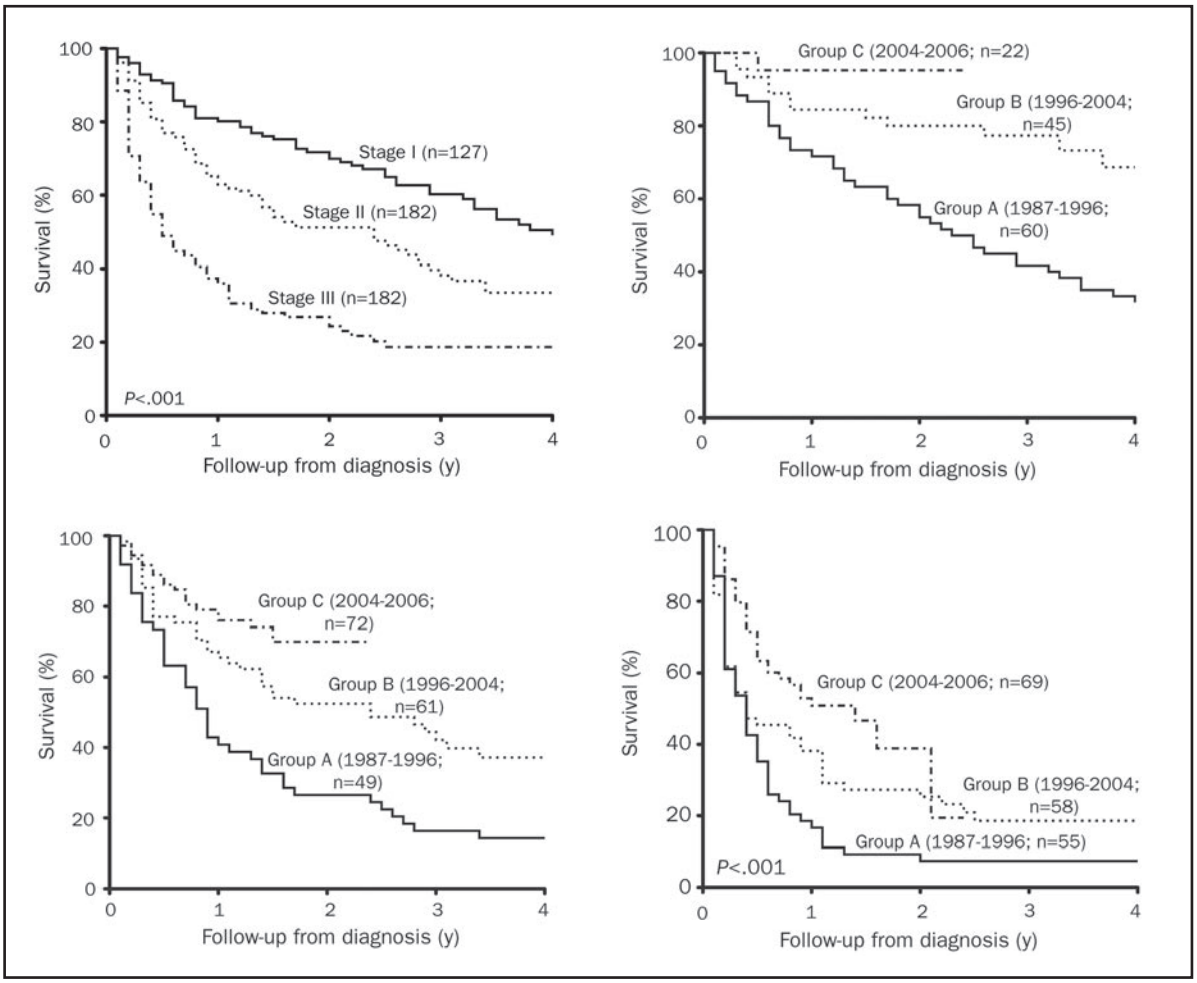

FIGURE 2. Upper left: Overall survival (OS) from diagnosis among 491 patients with available laboratory data, grouped according to the cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) staging system. The staging system uses a cutoff value for NT-proBNP of less than 332 ng/L and a cutoff value for cTnT of less than 0.035 μg/L. Depending on whether values were both low, high for only one, or high for both, patients were classified as having stage I, II, or III disease, respectively. The median OS from diagnosis for patients in stages I, II, and III was 4.0, 2.4, and 0.5 years, respectively (P<.001). Upper Right, Lower Left, Lower Right: Overall survival from diagnosis among patients in prognostic stages I, II, and III, respectively, with each stage divided into 3 groups according to the date of diagnosis (group A, 1987-1996; group B, 1996-2004; and group C, 2004-2006). Among patients with stage I disease, the median OS was not reached for group B or C and was 2.3 years (95% confidence interval, 1.4-3.3) for group A (upper right). Among patients with stage II disease, the median OS was not reached for the recent group and was 2.4 years for group B and 0.9 year for group A (lower left). Finally, among stage III patients, the most recent group had a median OS of 1.0 year compared with 0.4 year for both group A and group B (P<.001; lower right).

univariate logistic regression analysis, we identified factors that influenced the risk of 1-year mortality. The factors used in the regression analysis included septal thickness, cTnT, NT-proBNP, serum creatinine, serum uric acid, total bilirubin, alkaline phosphatase, serum free light-chain difference (calculated as the involved free light chain value minus the uninvolved free light chain value), β_2-microglobulin, and bone marrow plasma cell percentage. All were analyzed in a univariate fashion, and the best cutoff for each variable predicting 1-year mortality was identified. The individual variables were then dichotomized using the best cutoff and entered into the multivariate model. Using stepwise regression analysis, we found that a combination of cTnT greater than 0.01 μg/L, NT-proBNP greater than 4200 ng/L, and uric acid greater than 8.0 mg/dL best predicted the risk of death within 1 year of diagnosis. We first examined a group of 459 patients with all 3 variables available (training group). The 1-year mortality estimate for this cohort of patients was 40% (95% CI, 34%-44%), and the median OS was 20.4 months. The probability of death within 1 year for those with 0, 1, 2, and 3 risk factors was 19%, 37%, 61%, and 80%, respectively (P<.001; Figure 3, A).

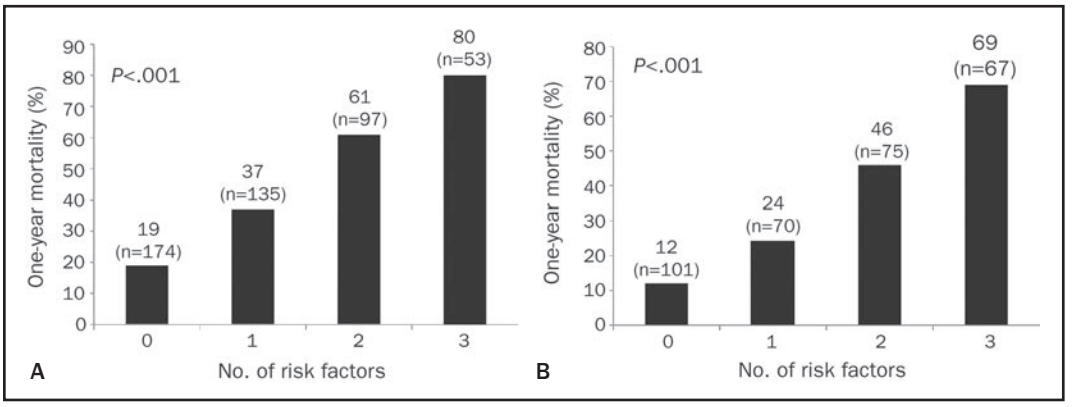

FIGURE 3. A, One-year mortality rates among patients with 0, 1, 2, or 3 risk factors for early mortality. The 3 risk factors were cardiac troponin T level greater than 0.01 μg/L, N-terminal pro-brain natriuretic peptide level greater than 4200 ng/L, and uric acid greater than 8.0 mg/dL. Patients with data available for all 3 variables (n=459) were included in this analysis. The probability of dying within 1 year for those with 0, 1, 2, and 3 risk factors was 19%, 37%, 61%, and 80%, respectively (*P*<.001). B, One-year mortality rates among patients with 0, 1, 2, or 3 risk factors for early mortality from among patients seen during 2006-2009. Patients with data available for all 3 variables (n=313) were included in this analysis. The probability of dying within 1 year for those with 0, 1, 2, and 3 risk factors was 12%, 24%, 46%, and 69%, respectively (*P*<.001).

To validate these findings, we examined a more recent cohort of 313 patients whose AL was diagnosed between September 2006 and August 2009. The characteristics of the training group and the validation group are presented in Table 2, and they appear to be comparable except for higher cardiac biomarker levels in the validation group. The 1-year mortality estimate for the validation group was 38% (95% CI, 33%-43%), and the median OS was 30.2 months. We then applied the risk-scoring system developed in the training group to the validation group. Of the 313 patients, 101, 70, 75, and 67 had 0, 1, 2, and 3 risk factors, respectively. The probability of dying within 1 year for those with 0, 1, 2, and 3 risk factors was 12%, 24%, 46%, and 69%, respectively(*P*<.001; Figure 3, B).

TABLE 2. **Comparison of Training and Validation Sets for Early Mortality Risk**[a,b]

	Training group (n=459)	Validation group (n=313)	*P* value[c]
Septal thickness (mm)	14	13	.70
Ejection fraction (%)	61	62	.60
Alkaline phosphatase (× ULN)	0.80	0.82	.80
Creatinine (mg/dL)	1.2	1.1	.10
Serum uric acid (mg/dL)	6.6	6.4	.40
Total bilirubin (mg/dL)	0.6	0.5	.05
Serum albumin (g/dL)	2.3	2.0	<.01
Urine albumin excretion (g/24 h)	0.6	0.8	.60
Free light-chain difference	18.4	19.6	.30
Troponin T (μg/L)	0.02	0.03	<.01
NT-proBNP (ng/L)	185	521	<.01

[a] NT-proBNP = N-terminal pro-brain natriuretic peptide; ULN = upper limit of normal. Data are provided as medians.
[b] SI conversion factors: To convert creatinine values to μmol/L, multiply by 88.4; to convert serum uric acid values to μmol/L, multiply by 59.485; to convert total bilirubin values to μmol/L, multiply by 17.104; to convert serum albumin values to g/L, multiply by 10.
[c] Wilcoxon signed rank test.

DISCUSSION

Primary systemic amyloidosis continues to be a challenge to treating physicians for a variety of reasons, including delays in diagnosis due to a lack of clinical suspicion, poor performance status of patients at the time of diagnosis, and limited treatment options.[3,27] The combination of melphalan and prednisone had been the mainstay of therapy until a decade or 2 ago, but several therapeutic options have become available in the past 10 to 15 years.[28,29] These include high-dose therapy and SCT, the combination of melphalan and dexamethasone, and more recently the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide used alone or in combination.[6-10,14-24,30,31] How much these individual interventions have changed the outcome of patients with AL remains unclear.

The current study carries 2 important messages. First, it highlights the improved survival in this disease during the past 3 decades. Unfortunately, the sickest patients have seen very little of this benefit, especially within the first year of diagnosis. These data also underscore the poor outcome of patients with AL in general, with a 5-year OS rate of 28% even among the most recent (1997-2006) group studied. In contrast, the 5-year OS of patients with newly

diagnosed myeloma seen during this time period was more than 40%.[13]

Although the scope of the current study is limited in terms of identifying the basis for this improvement over time, some conclusions can be drawn. Some of the survival improvement likely reflects an increased awareness of the disease, permitting earlier treatment. However, this is clearly not the whole story because our cohorts showed a trend for sicker patients in the most recent time periods, as defined by prognostic variables described here. Although this study was not designed to assess the role of SCT in treatment of AL, the continued trend toward improved survival observed even among patients who did not receive SCT provides indirect evidence that increased use of SCT alone cannot explain the trends seen here. The more widespread use of melphalan and dexamethasone as a standard of care for patients with AL who are ineligible for or decline SCT likely has contributed to the recent improvements. This is supported by the fact that survival further increased since 2003 among the last cohort of patients, temporally correlating with the initial publication of the results with this regimen.[16] Specific examination of this hypothesis is not possible within this group of patients because treatment details are incomplete.

The second important message is that early mortality in AL remains an obstacle to improving outcomes, with nearly half of the patients dying within a year of diagnosis. Studies, especially those in the context of SCT, have shown the impact of cardiac involvement on early mortality in this disease.[10,32] Previous studies have suggested that measures of cardiac dysfunction and injury, such as troponin and NT-proBNP levels, can be used to stratify risk in these patients.[26,33] Analysis of our patients enabled us to identify 3 laboratory measurements, namely cTnT, NT-proBNP, and uric acid, which together were able to identify patients with the highest risk of early mortality. We further validated this early mortality risk scoring system in a separate group of patients seen more recently, during 2006-2009.

The cardiac biomarkers cTnT and NT-proBNP have been studied extensively in the setting of cardiac ischemia and failure, but the utility of uric acid has only recently been appreciated.[34-38] Several studies have suggested that uric acid is a powerful prognostic factor in patients with cardiac failure and that uric acid may play a direct role in inducing myocardial damage. In the setting of AL, it is possible that uric acid is a surrogate marker for damage to additional organs, such as the kidney, potentially conferring additional prognostic value for this variable. Regardless, our early mortality scoring system can be used prospectively to identify those at risk of early death so that treatments can be risk-adapted and trials can be designed to enroll these patients to examine novel strategies.

CONCLUSION

Survival among patients with AL has improved during the past 3 decades, an improvement that appears to be ongoing. These trends likely represent the cumulative effect of earlier diagnosis, better risk assessment, better disease-specific therapies, and improved supportive care. The risk of early death remains high for patients with AL and should be the focus of future studies if outcome is to be further improved. More detailed studies should examine the precise causes of death in these patients so that future trials can be designed to address them.

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